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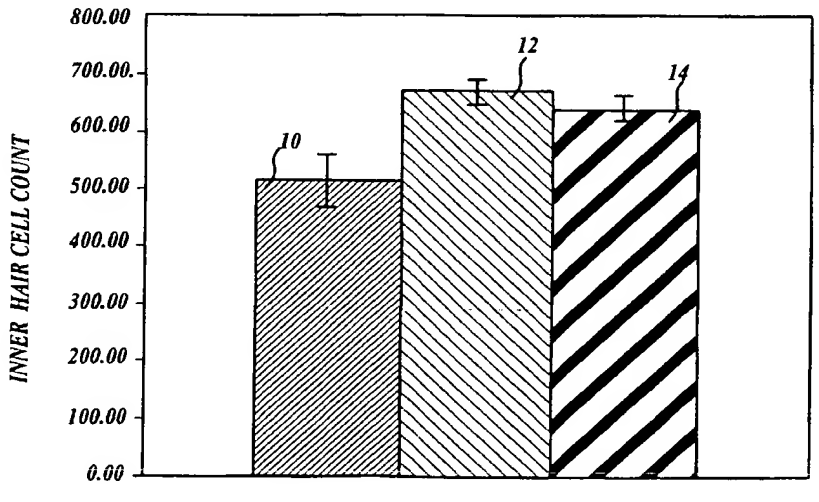


(57) Abstract: In one aspect, the present invention provides chemoprotectant compositions that each comprise at least two of the chemoprotectants disclosed herein. The chemoprotectant compositions of the invention are useful, for example, for ameliorating at least one adverse effect of chemotherapy.In another aspect, the present invention provides methods of ameliorating at least one adverse effect of chemotherapy, the methods each comprising the step of administering to a subject undergoing chemotherapy an amount of a chemoprotectant composition that is effective to ameliorate at least one adverse effect of the chemotherapy.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS AND COMPOSITIONS FOR AMELIORATING THE UNDESIRABLE EFFECTS OF CHEMOTHERAPY

FIELD OF THE INVENTION

The present invention relates to methods and compositions for ameliorating the undesirable effects of chemotherapy, such as chemotherapy that utilizes cisplatin.

BACKGROUND OF THE INVENTION

One approach to the treatment of cancer is chemotherapy in which one or more chemical substances that are toxic, or otherwise deleterious, to the cancerous cells are administered to an individual suffering from cancer. Unfortunately, most, if not all, chemotherapeutic agents cause undesirable effects that adversely affect the health of the patient.

By way of example, the chemotherapeutic agent cisplatin (*cis*-diamminedichloroplatinum) is a heavy metal complex, with platinum as the central atom surrounded by two chloride atoms and two ammonia molecules in the cis position. Cisplatin produces interstrand and intrastrand crosslinkage in DNA of rapidly dividing cells, thus preventing DNA, RNA, and/or protein synthesis.

Cisplatin is typically used (often in combination with other chemotherapeutic agents, such as paclitaxel, cyclophosphomide, vinblastine, doxorubicin and bleomycin) to treat patients having metastatic testicular tumors, metastatic ovarian tumors, carcinoma of the endometrium, bladder, head, or neck. Unfortunately, cisplatin causes numerous adverse effects, such as seizures, peripheral neuropathies, ototoxicity, hearing loss, deafness, vertigo, dizziness, blurred vision, nausea, vomiting, anorexia, diarrhea, constipation, myelosuppression, thrombocytopenia, anemia, neutropenia, and nephrotoxicity.

Thus, there remains a need for compositions and methods that ameliorate or eliminate the undesirable effects of chemotherapy. In particular, there remains a need for compositions and methods that ameliorate or eliminate one or more, or all, of the undesirable effects of cisplatin chemotherapy.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides chemoprotectant compositions that each comprise at least two of the chemoprotectants disclosed herein. The

chemoprotectant compositions of the invention are useful, for example, for ameliorating at least one adverse effect of chemotherapy.

In another aspect, the present invention provides pharmaceutical compositions that each include: (a) a chemoprotectant selected from the group consisting of methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaltCys, CellCys, OTCA, allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and 6-diSeCD; and (b) a chemotherapeutic agent.

In another aspect, the present invention provides methods of ameliorating at least one adverse effect of chemotherapy, the methods each comprising the step of administering to a subject undergoing chemotherapy an amount of a chemoprotectant composition that is effective to ameliorate at least one adverse effect of the chemotherapy. The chemoprotectant composition comprises one or more (such as at least two) of the chemoprotectants disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus concentration of cisplatin in the culture medium. The number of live cells was measured after culturing the cells for 24 hours in the presence of cisplatin.

FIGURE 2 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration (in units of μM) of N-acetyl-cysteine (NAC) in the culture medium. The viability of NuTu-19 cells cultured in the presence of N-acetylcysteine, but not in the presence of cisplatin, is shown by the upper graph. The

viability of NuTu-19 cells cultured in the presence of both N-acetylcysteine and cisplatin (at a concentration of 43 μM) is shown by the lower graph.

FIGURE 3 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of Ebselen in the culture medium. The viability of NuTu-19 cells cultured in the presence of Ebselen, but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of both Ebselen and cisplatin (at a concentration of 43 μM) is shown by the lower graph.

FIGURE 4 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of allopurinol in the culture medium. The viability of NuTu-19 cells cultured in the presence of allopurinol, but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of both allopurinol and cisplatin (at a concentration of 43 μM) is shown by the lower graph.

FIGURE 5 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of N-acetylcysteine in the culture medium. The viability of NuTu-19 cells cultured in the presence of N-acetylcysteine and Ebselen (at a concentration of 47 μM), but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of N-acetylcysteine, Ebselen (at a concentration of 47 μM) and cisplatin (at a concentration of 43 μM) is shown by the lower graph.

FIGURE 6 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of allopurinol in the culture medium. The viability of NuTu-19 cells cultured in the presence of allopurinol and Ebselen (at a concentration of 47 μM), but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of allopurinol and Ebselen (at a concentration of 47 μM) and cisplatin (at a concentration of 43 μM) is shown by the lower graph.

FIGURE 7 shows a graph showing the number of inner ear hair cells in rat cochlea that were cultured, *in vitro*, in the presence of 43 μM cisplatin (10), or 43 μM cisplatin plus 47 μM Ebselen (12), or 47 μM Ebselen (14).

FIGURE 8 shows the permanent threshold shift (PTS) in hearing at 8 kHz, 16 kHz, 24 kHz and 32 kHz of rats treated with saline and DMSO (vehicle control) (20),

or with cisplatin (at a dosage of 16 mg/kg body weight) in the presence of Ebselen (at a dosage of 16mg/kg body weight) (22). Ten cochlea were tested per treatment.

FIGURE 9 shows the permanent threshold shift (PTS) in hearing at 8 kHz, 16 kHz, 24 kHz and 32 kHz of rats treated with cisplatin (at a dosage of 16 mg/kg body weight) in the presence of allopurinol (at a dosage of 16 mg/kg body weight) (30), or in the presence of the combination of allopurinol (at a dosage of 8 mg/kg body weight) and Ebselen (at a dosage of 8 mg/kg body weight) (32). Four cochlea were tested per treatment.

FIGURE 10A shows the percentage of missing cochlear outer hair cells plotted against the distance from the apex of the cochlea in the left cochlea of a rat treated with the combination of cisplatin, saline and DMSO.

FIGURE 10B shows the percentage of missing cochlear outer hair cells plotted against the distance from the apex of the cochlea in the left cochlea of a rat treated with the combination of cisplatin and Ebselen.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

As used herein, the term "chemoprotectant" refers to a chemical substance that is capable of ameliorating at least one adverse effect of chemotherapy.

As used herein, the term "chemoprotectant composition" refers to a composition that includes at least one chemoprotectant, and may include more than one chemoprotectant. Chemoprotectant compositions may also include, in addition to one or more chemoprotectant(s), pharmaceutically acceptable carriers that facilitate administration of a chemoprotectant composition to a mammalian subject.

As used herein, the term "ameliorating at least one adverse effect of chemotherapy" includes: (a) reducing the magnitude and/or duration of at least one adverse effect of chemotherapy; and/or (b) completely eliminating at least one adverse effect of chemotherapy; and/or (c) preventing the onset of one or more adverse effect(s) of chemotherapy that would occur without administration of a chemoprotectant composition of the invention.

As used herein, the term "chemotherapeutic agent" is an agent that is administered to a mammalian subject to destroy, or otherwise adversely affect, cancer cells.

In one aspect the present invention provides methods for ameliorating at least one adverse effect of chemotherapy, the methods comprising the step of administering to a

subject undergoing chemotherapy an amount of a chemoprotectant composition that is effective to ameliorate at least one adverse effect of the chemotherapy. The methods of the invention are applicable to any mammalian subject, such as a human subject, undergoing any form of chemotherapy.

The chemoprotectant compositions can include one or more than one chemoprotectant. Unless stated otherwise, any isomeric or tautomeric form of any of the chemoprotectants disclosed herein can be used in the invention. Some chemoprotectants that can be included in chemoprotectant compositions of the invention include one or more sulfur-containing groups (such as sulfhydryl or thiol groups). Representative examples of chemoprotectants that include one or more sulfur-containing groups are: methionine; N-acetyl-DL-methionine; S-adenosylmethionine; cysteine; homocysteine; cystathione; cysteamine; N-acetylcysteine; glutathione; glutathione ethylester; glutathione diethylester; glutathione triethylester; cysteamine; N, N'-diacetyl-L-cystine (DiNAC); 2(R,S)-D-ribo-(1',2'3',4'- tetrahydroxybutyl)-thiazolidine-4(R)-carboxylic acid (RibCys); 2-alkylthiazolidine 2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)thiazolidine (RibCyst); 2(R,S)-D-gluco-(1',2',4',5'-Tetrahydroxypentyl-3'-O-D-galactopyranosyl)thiazolidine-4(R)-carboxylic acid (β-LactCys); 2(R,S)-D-gluco-(1',2',4',5'-Tetrahydroxypentyl-3'-O-α-D-galactopyranosyl)thiazolidine-4(R)-carboxylic acid (α-LactCys); 2(R,S)-D-gluco-(1',2',3',4'-Tetrahydroxypentyl-5'-O-α-D-galactopyranosyl)thiazolidine-4(R)-carboxylic acid (MeliCys); 2(R,S)-D-gluco-(1',2',4',5'-Tetrahydroxypentyl-3'-O-α–D-glucopyranosyl)thiazolidine-4(R)-carboxylic acid (MaltCys); 2(R,S)-D-gluco-(1',2',4',5'-Tetrahydroxypentyl-3'-O-β–D-glucopyranosyl) thiazolidine-4(R)-carboxylic acid (CellCys); and 2-oxo-L-thiazolidine-4-carboxylic acid (OTCA).

Allopurinol ($C_5H_4N_4O$) and its tautomers are also useful as chemoprotectants in the practice of the invention. The following representative allopurinol derivatives are useful as chemoprotectants in the practice of the invention: 1-methylallopurinol; 2-methylallopurinol; 5-methylallopurinol; 7-methylallopurinol; 1,5-dimethylallopurinol; 2,5-dimethylallopurinol; 1,7-dimethylallopurinol; 2,7-dimethylallopurinol; 5,7-dimethylallopurinol; 2,5,7-trimethylallopurinol; 1-ethoxycarbonylallopurinol; and 1-ethoxycarbonyl-5-methylallopurinol.

Other examples of chemoprotectants useful in the practice of the invention include: 2-phenyl-1,2-benzoisoselenazol-3(2H)-one (Ebselen), and 6A, 6B-diseleninic acid-6A', 6B'-selenium bridged β-cyclodextrin (6-diSeCD).

Table 1 sets forth representative effective dosage ranges for some of the chemoprotectants described herein. The chemoprotectants set forth in Table 1 are preferably administered orally or intravenously. The chemoprotectants set forth in Table 1 can be administered to a mammalian subject before, during or after administration of one or more chemotherapeutic agents to the mammalian subject. Thus, a mammalian subject typically receives one dose of chemoprotectant(s) for each dose of chemotherapeutic agent(s).

In some embodiments of the invention, one or more of the chemoprotectants set forth in Table 1 are administered to a mammalian subject at any time during a period extending from 18 hours before administration of one or more chemotherapeutic agents to the mammalian subject, to 18 hours after administration of one or more chemotherapeutic agents to the mammalian subject. In some embodiments of the invention, one or more of the chemoprotectants set forth in Table 1 are administered to a mammalian subject at any time during a period extending from one hour before administration of one or more chemotherapeutic agents to the mammalian subject, to one hour after administration of one or more chemotherapeutic agents to the mammalian subject. In some embodiments of the invention, one or more of the chemoprotectants set forth in Table 1 are administered to a mammalian subject at any time during a period extending from 10 minutes before administration of one or more chemotherapeutic agents to the mammalian subject, to ten minutes after administration of one or more chemotherapeutic agents to the mammalian subject. In some embodiments of the invention, one or more of the chemoprotectants set forth in Table 1 are administered to a mammalian subject concurrently with administration of one or more chemotherapeutic agents to the mammalian subject.

The abbreviation "mg" means milligrams.

TABLE 1

Compound(s)	Chemical name	Presently preferred range	Presently more preferred range	Presently most preferred range
NAM	N-acetyl-Methionine	5-5000mg/day	50-2000mg/day	500-1000mg/day
Methionine	Methionine	5-5000mg/day	50-2000mg/day	500-1000mg/day

Compound(s)	Chemical name	Presently preferred range	Presently more preferred range	Presently most preferred range
SAM	S-adenosyl-Methionine	5-5000mg/day	50-2000mg/day	500-1000mg/day
Cysteine	Cysteine	5-5000mg/day	50-2000mg/day	500-1000mg/day
NAC	N-acetyl-L-Cysteine	5-5000mg/day	50-2000mg/day	500-1000mg/day
DiNAC	N,N'-diacetyl-cystine	5-5000mg/day	50-2000mg/day	500-1000mg/day
homocysteine	homocysteine	5-5000mg/day	50-2000mg/day	500-1000mg/day
RibCyst	2-alkylthiazolidine, 2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)thiazolidine	5-5000mg/day	50-2000mg/day	500-1000mg/day
RibCys	2(R,S)-D-ribo-(1',2'3',4'-tetrahydroxybutyl)-thiazolidine-4(R)-carboxylic acid	5-5000mg/day	50-2000mg/day	500-1000mg/day
Cystathione	Cystathione	5-5000mg/day	50-2000mg/day	500-1000mg/day
Glutathione	Glutathione	5-5000mg/day	50-2000mg/day	500-1000mg/day
Glutathione ethyl ester	Glutathione ethyl ester	5-5000mg/day	50-2000mg/day	500-1000mg/day
Glutathione diethyl ester	Glutathione diethyl ester	5-5000mg/day	50-2000mg/day	500-1000mg/day
Glutathione triethyl ester	S-(1,2-dicarboxyethyl)glutathione triester	5-5000mg/day	50-2000mg/day	500-1000mg/day
Cysteamine	Cysteamine	5-5000mg/day	50-2000mg/day	500-1000mg/day
OTCA	2-oxo-L-thiazolidine-4-carboxylic acid	5-5000mg/day	50-2000mg/day	500-1000mg/day
Allopurinol	4-hydroxypyrazolo[3,4-d]pyrimidine	10-2400mg/day	50-1200mg/day	100-800mg/day
Ebselen	2-phenyl-1,2-benzoisoselenazol-3(2H)-one	5-5000mg/day	50-2000mg/day	500-1000mg/day
6-diSeCD	6A,6B-diseleninic acid-6A',6B'-selenium bridged beta-cyclodextrin	5-5000mg/day	50-2000mg/day	500-1000mg/day

The chemoprotectant compositions can include one, or more than one, chemoprotectant(s). Thus, chemoprotectant compositions of the invention can include any combination of any of the individual chemoprotectants described herein. In some embodiments of the chemoprotectant compositions that include more than one chemoprotectant, the chemoprotectant compositions are formulated to provide an effective dosage of the individual constituent chemoprotectants as set forth in Table 1. For example, as set forth in Table 1, the presently preferred dosage of both methionine and N-acetyl-methionine is from 5 mg to 5000 mg per day. Accordingly, some chemoprotectant compositions of the invention are formulated to provide methionine and N-acetyl-methionine each at a dosage of from 5 mg to 5000 mg per day.

In another aspect, the present invention provides chemoprotectant compositions that each comprise at least two (*e.g.*, two, three, four, five, six, seven, eight, nine or ten) of the individual chemoprotectants disclosed herein. For example, some chemoprotectant compositions include at least one chemoprotectant selected from Group A, at least one chemoprotectant selected from Group B, and at least one chemoprotectant selected from Group C, wherein Groups A, B and C include the following chemoprotectants:

Group A (glutathione or a glutathione precursor): methionine; N-acetyl-DL-methionine; S-adenosylmethionine; cysteine; N-acetylcysteine; glutathione; glutathione ethylester; glutathione diethylester; glutathione triethylester; DiNAC; RibCys; homocysteine; cystathione; cysteamine; OTCA and RibCyst.

Group B (strong antioxidants): allopurinol; 1-methylallopurinol; 2-methylallopurinol; 5-methylallopurinol; 7-methylallopurinol; 1,5-dimethylallopurinol; 2,5-dimethylallopurinol; 1,7-dimethylallopurinol; 2,7-dimethylallopurinol; 5,7-dimethylallopurinol; 2,5,7-trimethylallopurinol; 1-ethoxycarbonylallopurinol; and 1-ethoxycarbonyl-5-methylallopurinol.

Group C (Glutathione peroxidase mimic): Ebselen and 6-diSeCD.

The chemoprotectant compositions of the invention are useful, for example, for ameliorating at least one adverse effect of chemotherapy. The chemoprotectant compositions of the invention can be used in the methods of the invention for ameliorating at least one adverse effect of chemotherapy.

The chemoprotectant compositions of the invention can be formulated to provide a dosage that is effective to ameliorate one or more adverse effect(s) of chemotherapy

when administered to a subject undergoing chemotherapy. For example, in some embodiments the chemoprotectant compositions are formulated to provide an effective dosage of the individual chemoprotectants as set forth in Table 1.

Administration of the chemoprotectant compositions of the invention is accomplished by any effective route, *e.g.*, orally or parenterally. Methods of parenteral delivery include topical, intra-arterial, subcutaneous, intramedullary, intravenous, or intranasal administration. In addition to one or more chemoprotectants, the chemoprotectant compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and other compounds that facilitate administration of the chemoprotectant compositions to a mammalian subject undergoing chemotherapy. Further details on techniques for formulation and administration may be found in the latest edition of "Remington's Pharmaceutical Sciences" (Maack Publishing Co, Easton, PA).

Chemoprotectant compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art, in dosages suitable for oral administration. Such carriers enable the chemoprotectant compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, etc., suitable for ingestion by a subject.

Chemoprotectant compositions for oral use can be obtained, for example, through combination of one or more chemoprotectants with solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable excipients are carbohydrate or protein fillers. These include, but are not limited to, sugars, including lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins, such as gelatin and collagen. If desired, disintegrating or solubilising agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee

coatings for product identification or to characterise the quantity of active compound (*i.e.*, dosage).

Chemoprotectant compositions, which can be used orally, can be formulated, for example, as push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain chemoprotectants mixed with filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilisers. In soft capsules, the chemoprotectant(s) may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilisers.

Chemoprotectant compositions for parenteral administration include aqueous solutions of one or more chemoprotectants. For injection, the chemoprotectant compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of chemoprotectants may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Optionally, the suspension may also contain suitable stabilisers or agents, which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are typically used in the formulation. Such penetrants are generally known in the art.

The chemoprotectant compositions of the present invention may be manufactured in a manner similar to that known in the art (*e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilising processes). The chemoprotectant compositions may also be modified to provide appropriate release characteristics, *e.g.*, sustained release or targeted release, by conventional means (*e.g.*, coating).

The chemoprotectant compositions may be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric,

malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

After such chemoprotectant compositions formulated in an acceptable carrier have been prepared, they can be placed in an appropriate container and labeled for use.

The amount actually administered will be dependent upon the individual to which treatment is to be applied, and will preferably be an optimized amount such that the desired effect is achieved without significant side-effects. The determination of an effective dose is well within the capability of those skilled in the art. Of course, the skilled person will realize that divided and partial doses are also within the scope of the invention.

For any chemoprotectant composition, the effective dose can be estimated initially either in cell culture assays or in any appropriate animal model (*e.g.*, primate, rats and guinea pigs and other small laboratory animals). The animal model is also typically used to achieve a desirable concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans or other mammals.

Therapeutic efficacy and possible toxicity of chemoprotectant compositions can be determined by standard pharmaceutical procedures, in cell cultures or experimental animals (*e.g.*, ED_{50}, the dose therapeutically effective in 50% of the population; and LD_{50}, the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio ED_{50}/LD_{50}. Chemoprotectant compositions, which exhibit large therapeutic indices, are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for use in humans or other mammals. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage typically varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

In another aspect, the present invention provides pharmaceutical compositions that each include: (a) a chemoprotectant selected from the group consisting of methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaltCys, CellCys, OTCA, allopurinol, 1-methylallopurinol,

2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and 6-diSeCD; and (b) a chemotherapeutic agent.

Examples of chemotherapeutic agents useful in the pharmaceutical compositions of the invention include cisplatin, carboplatin, oxyplatin, vinblastine, doxorubicin, bleomycin, paclitaxel, cyclophosphomide, adriamycin, altretamine, methotrexate, and fluorouracil. In some embodiments, the chemotherapeutic agent includes platinum. Examples of chemotherapeutic agents that include platinum are cisplatin, carboplatin and oxyplatin. The pharmaceutical compositions are blended to provide a dose of one or more chemotherapeutic agents that is/are effective to kill, or otherwise adversely affect, cancer cells. The pharmaceutical compositions are also blended to provide a dose of one or more chemoprotectants effective to ameliorate at least one undesirable effect of the chemotherapeutic agent(s). Examples of desired daily doses of each of the foregoing chemoprotectants are set forth in Table 1. An example of a daily dosage of cisplatin is administration once per week at 50-200 mg/meter^2 per dose with 4 to 6 weeks of chemotherapy. The pharmaceutical compositions of the invention have the advantage that they simultaneously provide the recipient with a dosage of one or more chemotherapeutic agents, and a dosage of one or more chemoprotectants.

The chemoprotectant compositions, pharmaceutical compositions, and methods of the present invention can be used to ameliorate any adverse effect of chemotherapy utilizing any chemotherapeutic agent. Some chemoprotectant compositions, and pharmaceutical compositions, of the invention ameliorate most or all of the adverse effects of chemotherapy when used in accordance with the present invention. By way of example, the compositions and methods of the present invention can be used to ameliorate one, some, or all of the adverse effects of any of the following chemotherapeutic agents: cisplatin, carboplatin, oxyplatin, vinblastine, doxorubicin, bleomycin, paclitaxel, cyclophosphomide, adriamycin, altretamine, methotrexate, and fluorouracil. The principal adverse effects of the foregoing chemotherapeutic agents are: nephrotoxicity, neurotoxicity, ototoxicity, myelosuppression, alopecia, weight loss, vomiting, nausea and immunosuppression. The most effective chemoprotectant composition(s) of the invention for ameliorating one or more adverse effects of a specific

chemotherapeutic agent can be readily determined by routine experimentation by one of ordinary skill in the art.

The following examples merely illustrate the best mode now contemplated for practicing the invention, but should not be construed to limit the invention. All literature citations herein are expressly incorporated by reference.

EXAMPLE 1

This example shows that N-acetylcysteine, Ebselen and allopurinol, alone, or in combination, do not inhibit the ability of cisplatin to kill cultured NuTu-19 ovarian cancer tumor cells as measured using the MTS cell viability assay.

NuTu-19 cells were plated at a density of 3,000 cells per well in 96 well culture dishes, and incubated at 37°C, in the presence of 5% carbon dioxide, for 24 hours. N-acetylcysteine, Ebselen or allopurinol were incubated for one hour, or for four hours, with the NuTu-19 cells, then cisplatin was added to the cultures which were further incubated at 37°C, in the presence of 5% carbon dioxide, for 24 hours. The NuTu-19 cells were then rinsed with media and incubated in the presence of cisplatin for an additional 24 hours.

The NuTu-19 cells were then rinsed twice with phosphate buffered saline (PBS), then MTS assays were performed to measure the number of living cells. MTS is an abbreviation for (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium. The MTS assay is a colorimetric method for determining the number of viable cells based upon physiologic catabolism of MTS to a formazan product that is soluble in tissue culture medium. The absorbance of the formazan product at 490 nm can be measured directly from a 96 well plate using a plate reader. Increased absorbance at 490 nm correlates with increased production of formazan in a well. This is typically due to more viable cells present in a well.

FIGURE 1 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus concentration of cisplatin in the culture medium. The data set forth in FIGURE 1 show that cultured NuTu-19 ovarian cancer cells are killed after incubation for 24 hours in the presence of cisplatin.

FIGURE 2 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of N-acetylcysteine in the culture medium. The viability of NuTu-19 cells cultured in the presence of N-acetylcysteine, but not in the

presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of both N-acetylcysteine and cisplatin (at a concentration of 43 μM) is shown by the lower graph. The data set forth in FIGURE 2 shows that N-acetylcysteine does not inhibit the ability of cisplatin to kill NuTu-19 ovarian cancer tumor cells in culture.

FIGURE 3 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of Ebselen in the culture medium. The viability of NuTu-19 cells cultured in the presence of Ebselen, but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of both Ebselen and cisplatin (at a concentration of 43 μM) is shown by the lower graph. The data set forth in FIGURE 3 shows that Ebselen does not inhibit the ability of cisplatin to kill NuTu-19 ovarian cancer tumor cells in culture.

FIGURE 4 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of allopurinol in the culture medium. The viability of NuTu-19 cells cultured in the presence of allopurinol, but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of both allopurinol and cisplatin (at a concentration of 43 μM) is shown by the lower graph. The data set forth in FIGURE 4 shows that allopurinol does not inhibit the ability of cisplatin to kill NuTu-19 ovarian cancer tumor cells in culture.

FIGURE 5 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of N-acetyl-cysteine in the culture medium. The viability of NuTu-19 cells cultured in the presence of N-acetyl-cysteine and Ebselen (at a concentration of 47 μM), but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of N-acetyl-cysteine, Ebselen (at a concentration of 47 μM) and cisplatin (at a concentration of 43 μM) is shown by the lower graph. The data set forth in FIGURE 5 shows that the combination of N-acetyl-cysteine and Ebselen does not inhibit the ability of cisplatin to kill NuTu-19 ovarian cancer tumor cells in culture.

FIGURE 6 shows a plot of the percentage of live, cultured, NuTu-19 ovarian cancer cells versus the concentration of allopurinol in the culture medium. The viability of NuTu-19 cells cultured in the presence of allopurinol and Ebselen (at a concentration of 47 μM), but not in the presence of cisplatin, is shown by the upper graph. The viability of NuTu-19 cells cultured in the presence of allopurinol and Ebselen (at a

concentration of 47 μM) and cisplatin (at a concentration of 43 μM) is shown by the lower graph. The data set forth in FIGURE 6 shows that the combination of allopurinol and Ebselen does not inhibit the ability of cisplatin to kill NuTu-19 ovarian cancer tumor cells in culture.

EXAMPLE 2

This Example shows that Ebselen protects inner ear hair cells from damage by cisplatin *in vitro*.

Three cochlea per treatment, obtained from P3-4 mouse pups, were cultured in 0.4 micrometer MilliCell-CM inserts with NeuroBasal A medium plus B27 supplement. After 24 hours in culture Ebselen was added to the medium, incubated for ten minutes, and then cisplatin was added to the medium at a final concentration of 43 μM. A first control treatment included 43 μM cisplatin. A second control treatment included 47 μM Ebselen without the addition of cisplatin. All cultures were incubated for 24 hours at 37°C in 5% carbon dioxide.

The explants were then harvested, fixed, and stained with calbindin (which detects hair cells) and DAPI (4',6-Diamindino-2-phenylindole; for detection of nuclear DNA). FIGURE 7 shows the number of inner ear hair cells in mice cochlea that were cultured, *in vitro*, in the presence of 43 μM cisplatin (10), or 43 μM cisplatin plus 47 μM Ebselen (12), or 47 μM Ebselen (14). The data set forth in FIGURE 7 shows that Ebselen protects inner ear hair cells from damage by cisplatin *in vitro*.

The concentrations of cisplatin and Ebselen used in the experiments described in this Example are the same concentrations of cisplatin and Ebselen that were used in the cell culture assays described in Example 1. Thus, the experiments reported in Example 1 and Example 2 together show that, at the concentration utilized in these experiments, Ebselen does not protect NuTu-19 ovarian cancer tumor cells from the toxic effects of cisplatin, but does protect inner ear hair cells from the toxic effects of cisplatin.

EXAMPLE 3

This Example shows that Ebselen, and the combination of Ebselen and allopurinol, protect rat inner ear hair cells from damage by cisplatin *in vivo*.

Auditory Evoked Brainstem Response (ABR) was used to assess hearing in rats before and after exposure to cisplatin and chemoprotectants. Ebselen or DMSO (control

vehicle) were introduced intraperitoneally into rats one hour before intraperitoneal administration of cisplatin at a dosage of 16 mg/kg body weight. Seventy two hours after delivery of cisplatin, ABR data were collected, animals were sacrificed, cochleae were collected, dissected, stained with FITC-phalloidin (to detect F-Actin in hair cells), and DAPI (to detect nuclear DNA).

FIGURE 8 shows the permanent threshold shift (PTS) in hearing, at 8 kHz, 16 kHz, 24 kHz and 32 kHz, of rats treated with cisplatin (at a dosage of 16 mg/kg body weight) in the presence of Ebselen (at a dosage of 16mg/kg body weight) (22), or in the presence of saline and DMSO (control) (20). Ten cochlea were tested per treatment. The PTS is a measure of hearing loss. The data presented in FIGURE 8 show that the PTS is less (*i.e.*, there is less hearing loss) in rats treated with the combination of Ebselen and cisplatin, compared to rats treated with cisplatin without Ebselen.

FIGURE 9 shows the permanent threshold shift (PTS) in hearing, at 8 kHz, 16 kHz, 24 kHz and 32 kHz, of rats treated with cisplatin (at a dosage of 16 mg/kg body weight) in the presence of allopurinol (at a dosage of 16 mg/kg body weight) (30), or in the presence of the combination of allopurinol (at a dosage of 8 mg/kg body weight) and Ebselen (at a dosage of 8 mg/kg body weight) (32). Four cochlea were tested per treatment. The data presented in FIGURE 9 show that the PTS is less in rats treated with the combination of Ebselen and allopurinol, compared to rats treated with allopurinol without Ebselen.

Additionally, cochleae were excised from rats treated with the combination of cisplatin and Ebselen as described in this Example. Cochleae were also excised from rats treated with cisplatin and saline and DMSO (control). The number of outer auditory hair cells in the excised cochlea were counted at intervals of 0.1 mm along the cochlea. Representative results from a control rat and a treated rat are shown in FIGURE 10A and FIGURE 10B, respectively. The data presented in FIGURE 10A and FIGURE 10B show that the percentage of outer hair cells missing in cochleae from rats treated with the combination of cisplatin and Ebselen is less than the percentage of outer hair cells missing in cochleae from rats treated with cisplatin, but not with Ebselen.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A chemoprotectant composition that comprises at least two chemoprotectants selected from the group consisting of methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaltCys, CellCys, OTCA, allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and 6-diSeCD.

2. A chemoprotectant composition of Claim 1 comprising at least two chemoprotectants selected from the group consisting of allopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and N-acetylcysteine.

3. A chemoprotectant composition of Claim 1 comprising allopurinol and 2-phenyl-1,2-benzoisoselenazol-3(2H)-one.

4. A chemoprotectant composition of Claim 1 comprising allopurinol and N-acetylcysteine.

5. A chemoprotectant composition of Claim 1 comprising 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and N-acetylcysteine.

6. A method of ameliorating at least one adverse effect of chemotherapy, the method comprising the step of administering to a subject undergoing chemotherapy an amount of a chemoprotectant composition that is effective to ameliorate at least one adverse effect of the chemotherapy, said chemoprotectant composition comprising a chemoprotectant selected from the group consisting of: L-methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester,

glutathione triethyl lester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaliCys, CellCys, OTCA, allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and 6-diSeCD.

7. A method of Claim 6 wherein said chemoprotectant composition comprises a chemoprotectant selected from the group consisting of allopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and N-acetylcysteine.

8. A method of Claim 6 wherein said chemoprotectant composition comprises allopurinol and 2-phenyl-1,2-benzoisoselenazol-3(2H)-one.

9. A method of Claim 8 wherein said allopurinol is administered in an amount of from 10 to 2400mg/day, and said 2-phenyl-1,2-benzoisoselenazol-3(2H)-one is administered in an amount of from 5 to 5000 mg/day.

10. A method of Claim 6 wherein said chemoprotectant composition comprises allopurinol and N-acetylcysteine.

11. A method of Claim 10 wherein said allopurinol is administered in an amount of from 10 to 2400 mg/day, and said N-acetylcysteine is administered in an amount of from 5 to 5000 mg/day.

12. A method of Claim 6 wherein said chemoprotectant composition comprises 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and N-acetylcysteine.

13. A method of Claim 12 wherein said 2-phenyl-1,2-benzoisoselenazol-3(2H)-one is administered in an amount of from 5-5000 mg/day, and said N-acetylcysteine is administered in an amount of from 5 to 5000 mg/day.

14. A chemoprotectant composition comprising:

(a) a chemoprotectant selected from the group consisting of methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, DiNAC, RibCys, homocysteine, cystathione, cysteamine, OTCA and RibCyst;

(b) a chemoprotectant selected from the group consisting of allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2;5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, and 1-ethoxycarbonyl-5-methylallopurinol; and

(c) a chemoprotectant selected from the group consisting of Ebselen and 6-diSeCD.

15. A pharmaceutical composition comprising:

(a) a chemoprotectant selected from the group consisting of methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaltCys, CellCys, OTCA, allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1,2-benzoisoselenazol-3(2H)-one, and 6-diSeCD; and

(b) a chemotherapeutic agent.

16. A method of Claim 15 wherein said chemotherapeutic agent comprises platinum.

17. A method of Claim 16 wherein said chemotherapeutic agent comprises cisplatin.

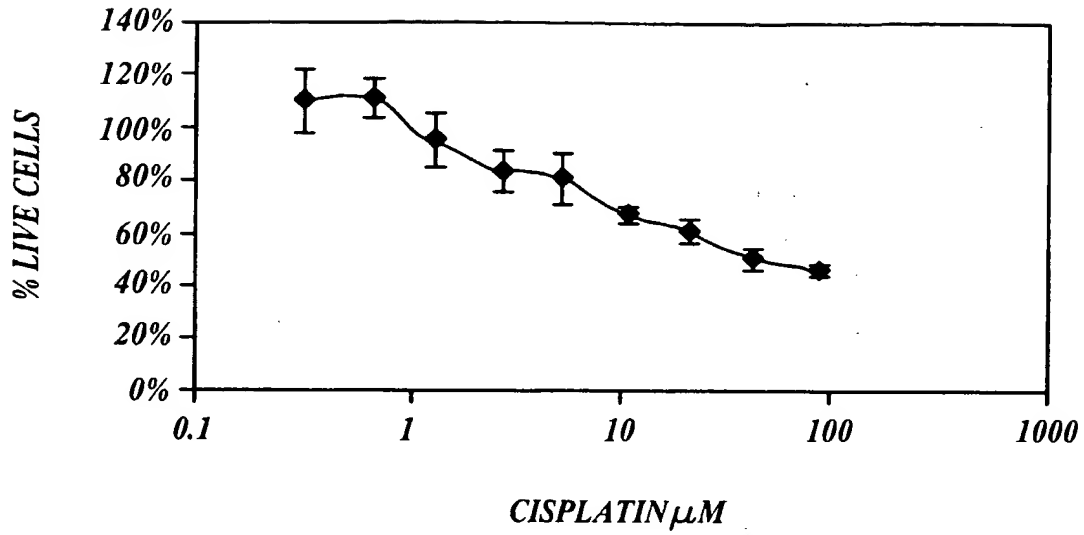
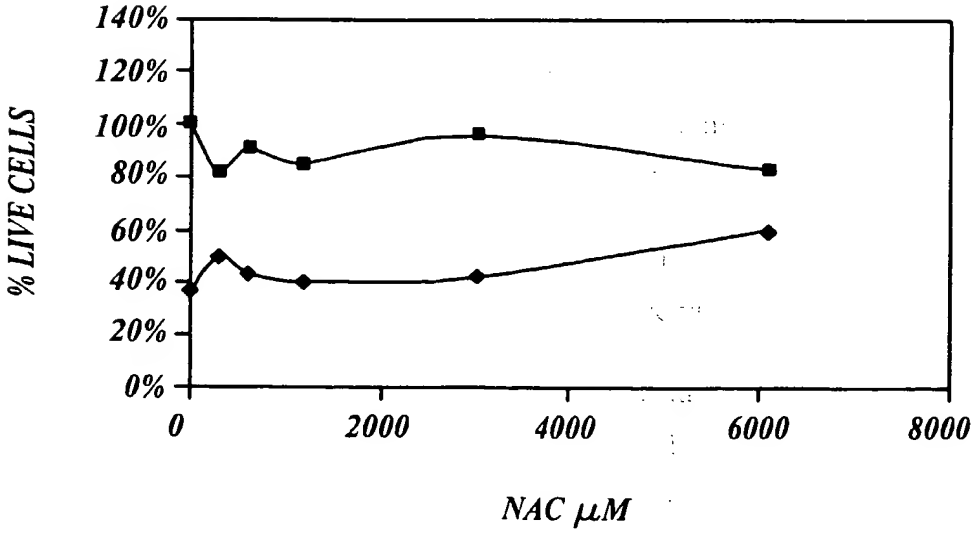

140%
120%
100%
80%
60%
40%
20%
0%
% LIVE CELLS
0.1
1
10
100
1000
CISPLATIN μM

Fig. 1.


140%
120%
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0%
% LIVE CELLS
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2000
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6000
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NAC μM

Fig. 2.

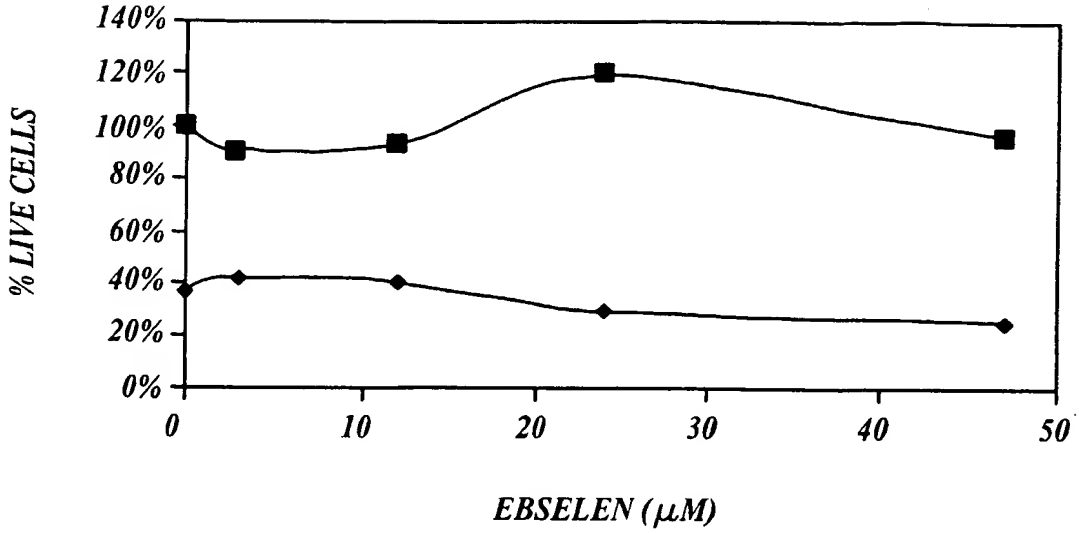

Fig.3.

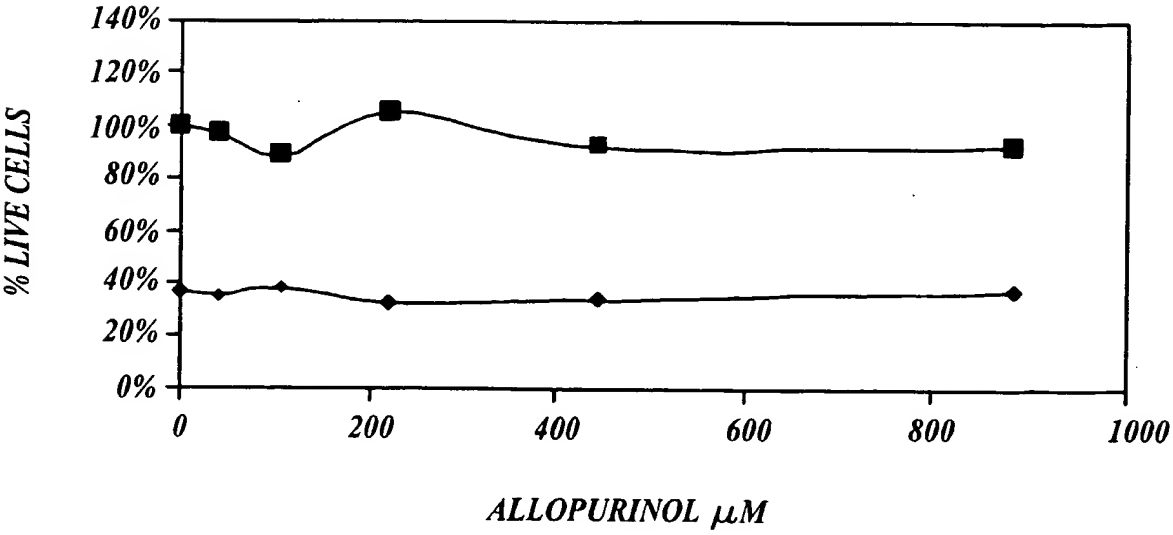

Fig.4.

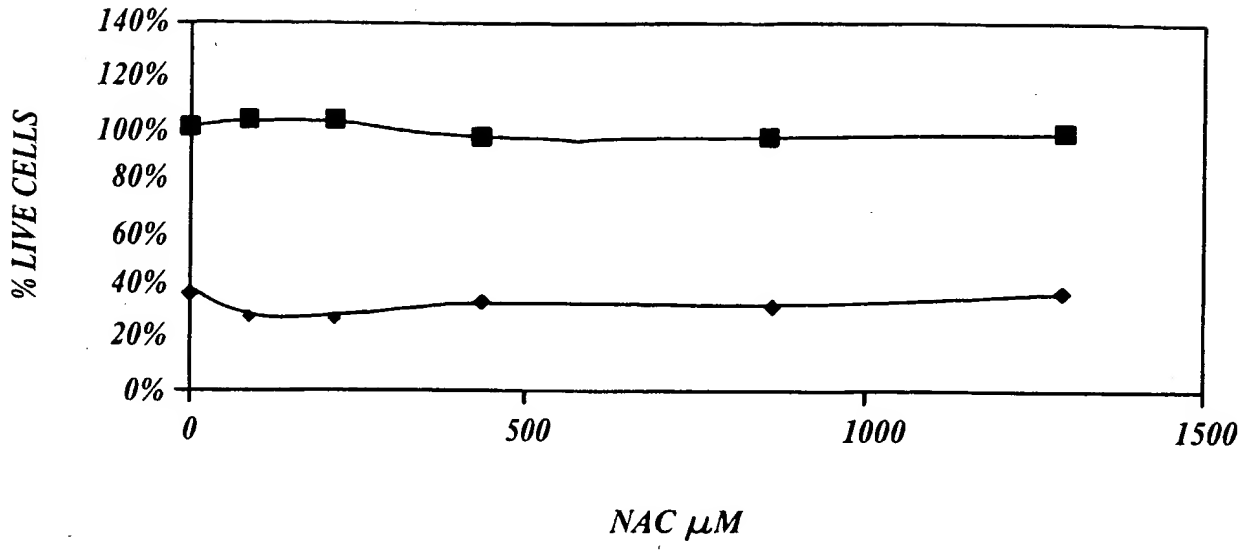

Fig. 5.

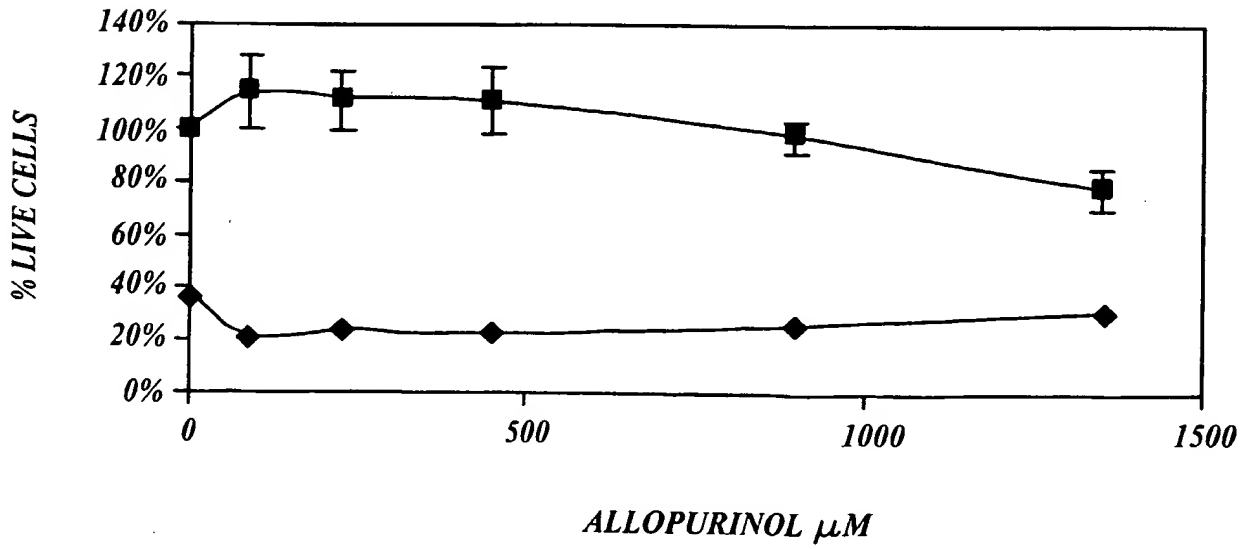

Fig. 6.

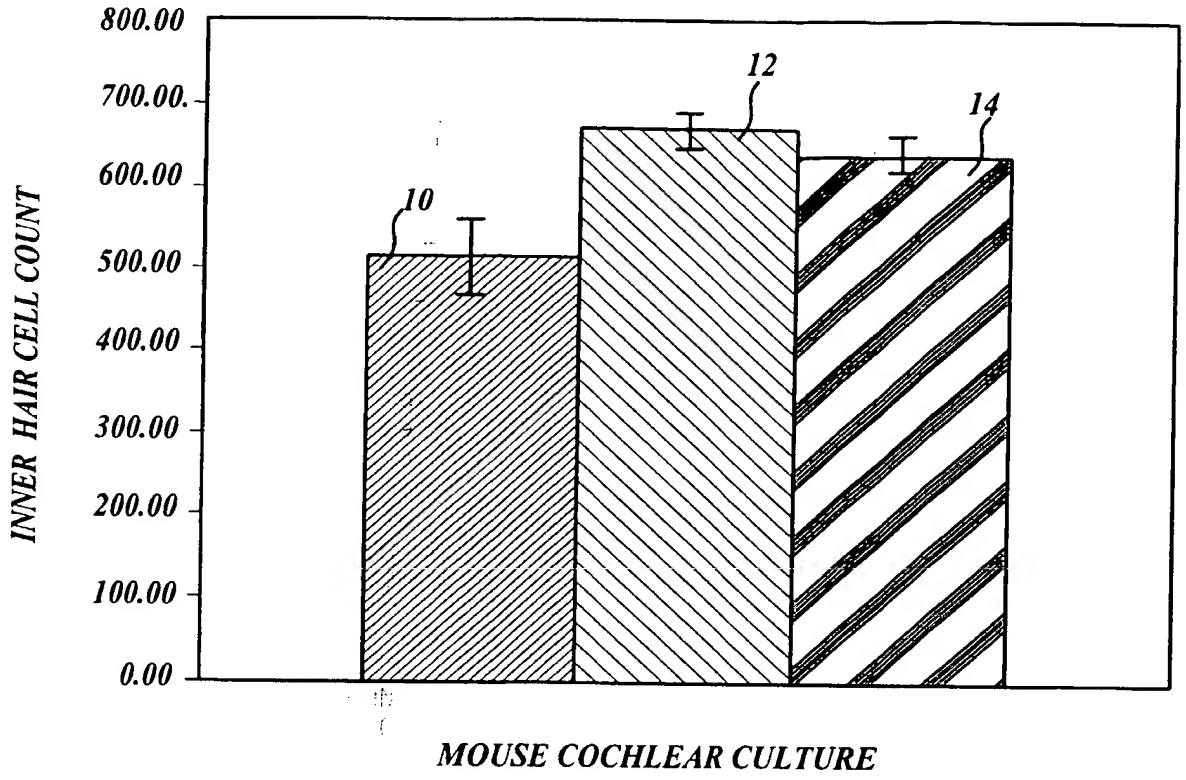

Fig. 7.

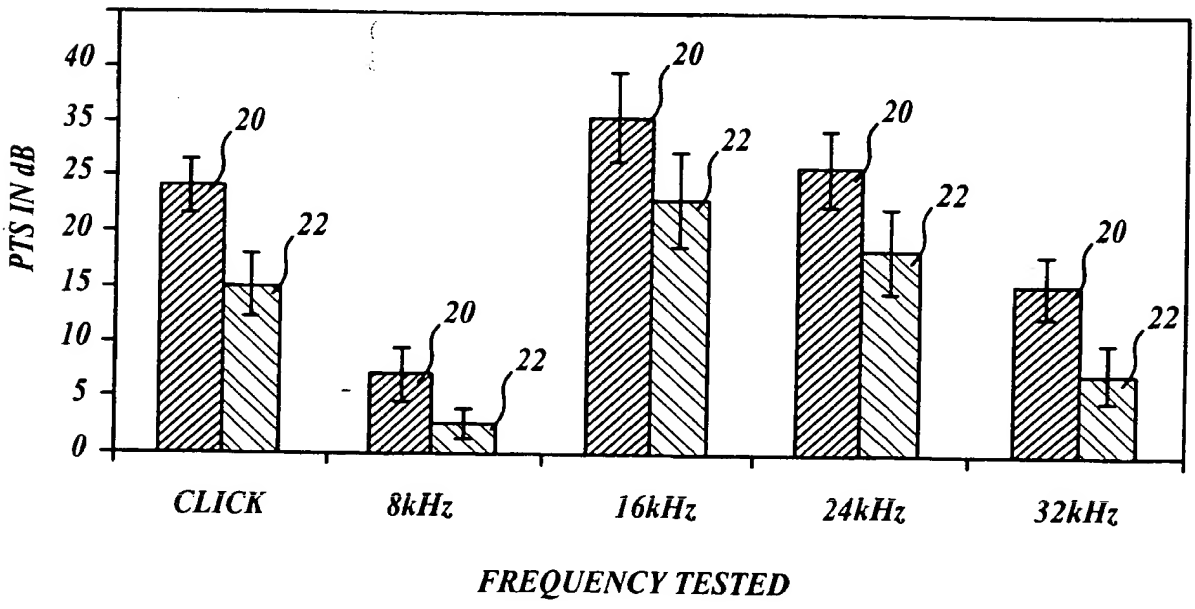

Fig. 8.

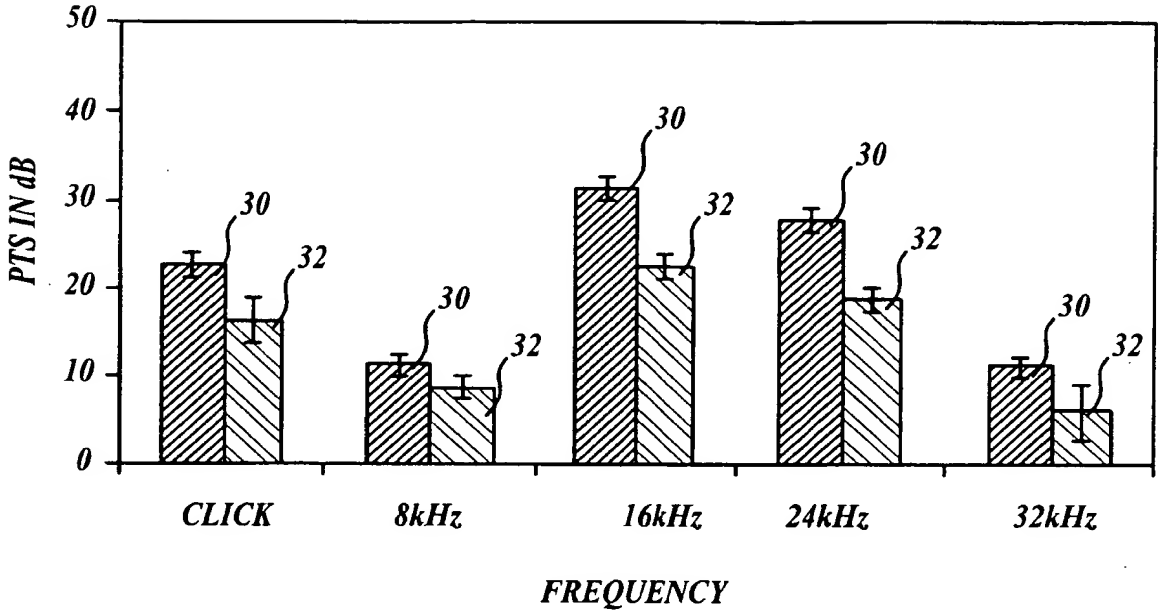

Fig. 9.

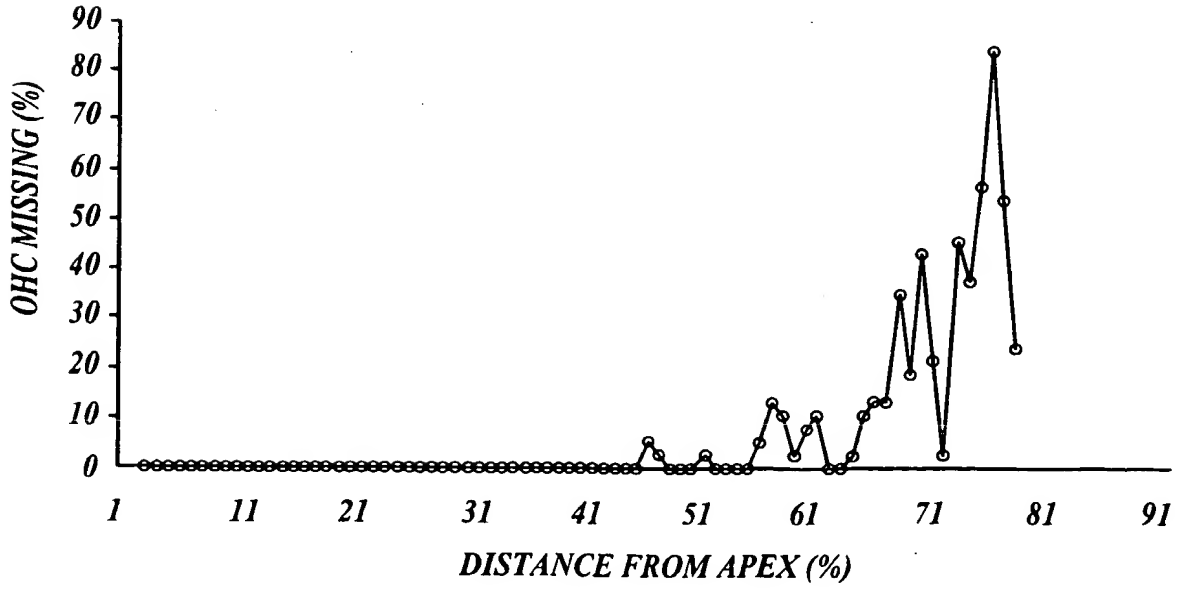

Fig. 10A.

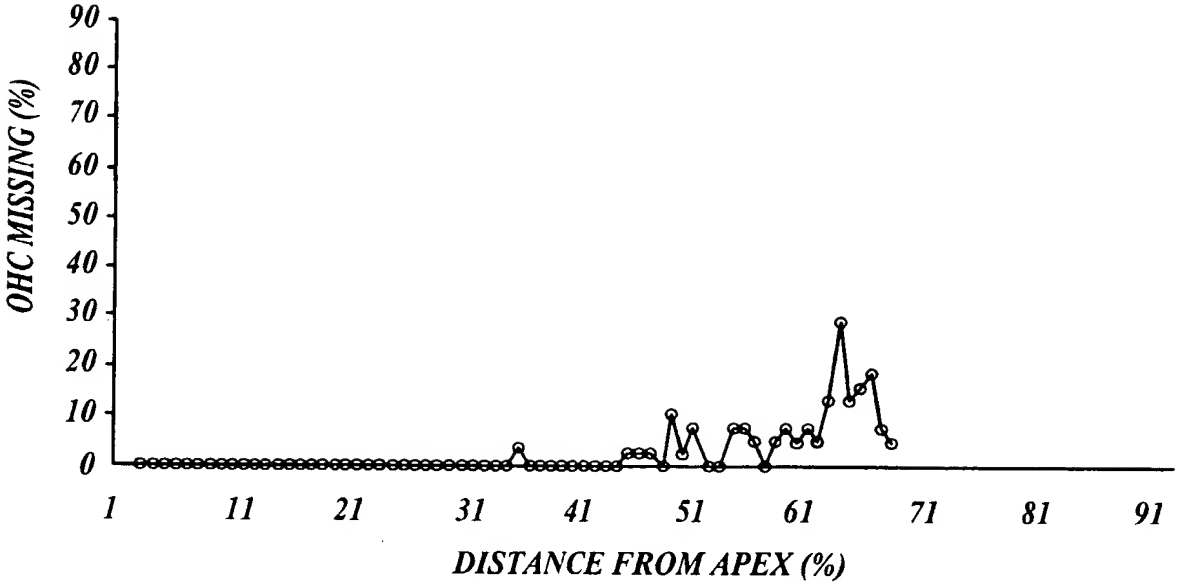

Fig. 10B.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/045334 A3

(54) Title: METHODS AND COMPOSITIONS FOR AMELIORATING THE UNDESIRABLE EFFECTS OF CHEMOTHERAPY

(57) Abstract: In one aspect, the present invention provides chemoprotectant compositions that each comprise at least two of the chemoprotectants disclosed herein. The chemoprotectant compositions of the invention are useful, for example, for ameliorating at least one adverse effect of chemotherapy. In another aspect, the present invention provides methods of ameliorating at least one adverse effect of chemotherapy, the methods each comprising the step of administering to a subject undergoing chemotherapy an amount of a chemoprotectant composition that is effective to ameliorate at least one adverse effect of the chemotherapy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38279

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/41, 31/195, 38/51, 38/52, 38/53
US CL : 514/269, 49, 360, 562
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 61K 31/41, 31/195, 38/51, 38/52, 38/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, No. 1998:675988, FERRER et al. 'Allopurinol and N-acetylcysteine Avoid 60% of Intestinal Necrosis in an Ischemia-Reperfusion Experimental Model,' abstract, Transplantation Proceedings, 1998, 30(6), 2672.	1, 2, 4
X	Database HCAPLUDS on STN, No. 1988:504365, COTGREAVE et al. 'The Anti-Inflammatory Activity of Ebselen but not Thiols in Experimental Alveolitis and Bronchiolitis,' abstract, AGents and Actions, 1988, 24 (3-4), 313-19.	1-5
X	Database HCAPLUS on STN, No. 1988:12394, COTGREAVE et al. 'Lung Protection by Thiol-Containing Antioxidants,' abstract, Clinical Respiratory, 1987, 23 (4), 275-7.	1-5
X	Database MEDLINE on STN, No. 1998270546, VERMEULEN et al. 'Toxicity of Fortemustine in Rat Hepatocytes and Mechanism-Based Protection Against It,' abstract,	1-6
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Y	CHEMICO-BIOLOGICAL INTERACTIONS, (1998 Apr 3) 110 (3) 139-58.	7-17
X	Database MEDLINE on STN, No. 92378712, PRITSOS et al. 'PZ-51 (Ebselen) in Vivo Protection Against Adriamycin-Induced Mouse Cardiac and Hepatic Lipid Peroxidation	1-7, 12-13
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Y	and Toxicity,' abstract, BIOCHEMICAL PHARMACOLOGY, (1992 Aug 18) 44 (4) 839-41.	8-11, 14-17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2003 (13.06.2003)	18 AUG 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Zoreh Fay Telephone No. 703-308-1235

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database MEDLINE on STN, No. 91309185, GUSTAFSON et al. 'Inhibition of Mitomycin C's Aerobic Toxicity by the Seleno-Organic Antioxidant PZ-51,' abstract, CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1991) 28 (3) 228-30.	1-7, 12-13
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Y		8-11, 14-17

INTERNATIONAL SEARCH REPORT

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Continuation of B. FIELDS SEARCHED Item 3:
STN ONLINE
search terms: allopurinol, 2-pheny-1,2-benzoisoselenazol-3(2H)-one, ebselen, N-acetylcysteine, platinum, cisplantin, glutathione